

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 12561030	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/AU2005/000098	International filing date (<i>day/month/year</i>) 28 January 2005	(Earliest) Priority Date (<i>day/month/year</i>) 30 January 2004
Applicant PEPLIN BIOLIPIDS PTY LTD et al		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 11 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. **Certain claims were found unsearchable** (See Box No. II).

3. **Unity of invention is lacking** (See Box No. III).

4. With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.

as selected by this Authority, because the applicant failed to suggest a figure.

as selected by this Authority, because this figure better characterizes the invention.

- b. none of the figures is to be published with the abstract.

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

IAP5 Rec'd PCT/PTO 28 JUL 2006

1. Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: **1 to 11 and 13 to 19, also Claim 12 in part.**

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See additional sheet.

3. Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2005/000098

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. ⁷: C07C 233/49, 323/52, 59/60, 409/42, 409/16, 409/04, 51/367; A61K 31/20, 31/19, 31/16; A61P 3/06, 9/10, 35/00, 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See electronic data bases below.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN Files Registry, CA: structure searches combined with search terms pkc, kinase, inflamm?, immunosupp?, pain, analges?, nf.kappa.b and the like. File Medline search terms: PUFA, fatty acid, nf.kappa.b, pkc and the like.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 1996/011908 A (PEPTIDE TECHNOLOGY LIMITED et al.) 25 April 1996. See whole document.	12
X	WO 1996/013507 A (PEPTIDE TECHNOLOGY LIMITED et al.) 9 May 1996. See whole document.	12
X	WO 1997/038688 A (PEPTIDE TECHNOLOGY PTY LIMITED et al.) 23 October 1997. See whole document.	12

 Further documents are listed in the continuation of Box C See patent family annex

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
6 April 2005Date of mailing of the international search report
15 APR 2005Name and mailing address of the ISA/AU
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2005/000098

C (Continuation).

DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2001/021172 A (WOMEN'S AND CHILDREN'S HOSPITAL ADELAIDE) 29 March 2001. See whole document.	12
X	WO 2001/021575 A (WOMEN'S AND CHILDREN'S HOSPITAL ADELAIDE) 29 March 2001. See whole document.	12
X	WO 1990/008130 A (FOLLIGEN BUDAPEST LTD) 26 July 1990. See whole document.	12
X	WO 2002/094764 A (CRODA INTERNATIONAL PLC) 28 November 2002. See whole document.	12
X	WO 2003/007876 A (UNIVERSITY OF MASSACHUSETTS) 30 January 2003. See whole document.	12
X	WO 2003/006007 A (RESEARCH & INNOVATION SOC. COOP. A R. L.) 23 January 2003. See whole document.	12
X	AU 200022459 A (L'OREAL) 19 October 2000. See whole document.	12
X	US 5151534 A (B. SHROOT et al.) 29 September 1992. See whole document.	12
X	WO 1999/058122 A (THIA MEDICA AS) 18 November 1999. See whole document.	12
X	WO 1999/058121 A (THIA MEDICA AS) 18 November 1999. See whole document.	12
X	WO 1999/058123 A (THIA MEDICA AS) 18 November 1999. See whole document.	12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2005/000098

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2002/043728 A (THIA MEDICA AS) 6 June 2002. See whole document.	12
X	WO 1997/003663 A (R. BERGE et al.) 6 February 1997. See whole document.	12
X	EP 345038 A (NORSK HYDRO AS) 6 December 1989. See whole document.	12
X	WO 1999/058120 A (R. BERGE) 18 November 1999. See whole document.	12
X	B. BJORNDAL et al., "Nuclear import of factors involved in signalling is inhibited in C3H/10T1/2 cells treated with tetradecylthioacetic acid", <i>J. Lipid Res.</i> , 43, 2002, pp. 1630-40. See whole document.	12
X	WO 2001/068582 A (THIA MEDICA AS) 20 September 2001. See whole document.	12
X	B. S. ROBINSON et al., "Inhibition of Neutrophil Leukotriene B4 Production by a Novel Synthetic N-3 Polyunsaturated Fatty Acid Analogue, β -Oxa 21:3n-3", <i>J. Immunol.</i> , 2003, 171(9), pp. 4773-9. See whole document.	12
X	M. COSTABILE et al., "A Novel Long Chain Polyunsaturated Fatty Acid, β -Oxa 21:3n-3, Inhibits T Lymphocyte Proliferation, Cytokine Production, Delayed-Type Hypersensitivity, And Carrageenan-Induced Paw Reaction And Selectively Targets Intracellular Signals", <i>J. Immunol.</i> , 2001, 167(7), pp. 3980-7. See whole document.	12
X	A. FERRANTE et al., "Neutrophil Migration Inhibitory Properties of Polyunsaturated Fatty Acids. The Role Of Fatty Acid Structure, Metabolism, And Possible Second Messenger Systems", <i>J. Clin. Invest.</i> , 1994, 93, pp. 1063-70. See whole document.	12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2005/000098

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	B. M. FORMAN et al., "Hypolipidemic Drugs, Polyunsaturated Fatty Acids, And Eicosanoids Are Ligands For Peroxisome Proliferator-Activated Receptors α and δ ", Proc. Natl. Acad. Sci. USA, 94, 1997, pp. 4312-17. See whole document.	12
X	Z. H. HUANG et al., "n 6 and n 3 Polyunsaturated fatty acids stimulate translocation of protein kinase C α , - β I, - β II and - ϵ and enhance agonist-induced NADPH oxidase in macrophages", Biochem. J., 325, 1997, pp. 553-7. See whole document.	12
X	T. E. NOVAK et al., "NF- κ B inhibition by ω -fatty acids modulates LPS-stimulated macrophage TNF- α transcription", Am. J. Physiol. Lung Cell Mol. Physiol., 284: L84-L89, 2003. See whole document.	12
X	A. DENYS et al., "Eicosapentaenoic acid and docosahexaenoic acid modulate MAP kinase (ERK1/ERK2) signalling in human T cells", J. Lipid Res., 42, 2001, pp. 2015-20. See whole document.	12
X	B. A. NARAYANAN et al., "Modulation of Inducible Nitric Oxide Synthase and Related Proinflammatory Genes by the Omega-3 Fatty Acid Docosahexaenoic Acid in Human Colon Cancer Cells", Cancer Res., 63, 2003, pp. 972-9. See whole document.	12
X	M. ZEYDA et al., "Suppression Of T Cell Signalling By Polyunsaturated Fatty Acids: Selectivity In Inhibition Of Mitogen Activated Protein Kinase And Nuclear Factor Activation", J. Immunol., 2003, 170, pp. 6033-9. See whole document.	12
X	J. V. FERRANTE et al., "Altered Responses Of Human Macrophages To Lipopolysaccharide By Hydroperoxy Eicosatetraenoic Acid, Hydroxy Eicosatetraenoic Acid, And Arachidonic Acid. Inhibition Of Tumor Necrosis Factor Production", J. Clin. Invest., 1997, 99, pp. 1445-52. See whole document.	12
X	Chemical Abstract 139:374536 & P. AUKRUST et al., "Immunomodulating effects of 3-thia fatty acids in activated peripheral blood mononuclear cells", Eur. J. Clin. Invest., 2003, 33(5), 426-433. See abstract and CAS RN 2921-20-2 (tetradecylthioacetic acid).	12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2005/000098

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S. M. HUANG et al., "Identification of a new class of molecules, the arachidonyl amino acids, and characterisation of one member that inhibits pain", <i>J. Biol. Chem.</i> , 2001, 276(46), pp. 42639-44. See whole document.	12
X	Chemical Abstract 138:268923 & J. J. PRUSAKIEWICZ et al., "Selective oxygenation of N-arachidonylglycine by cyclooxygenase-2", <i>Biochem. Biophys. Res. Commun.</i> , 2002, 296(3), 612-617. See abstract and CAS RN 179113-91-8, 338950-49-5, 338950-56-4	12
X	B. DEVADAS et al., "Substrate specificity of <i>Saccharomyces cerevisiae</i> myristoyl-CoA:protein N-myristoyltransferase. Analysis of fatty acid analogs containing carbonyl groups, nitrogen heteroatoms, and nitrogen heterocycles in an in vitro enzyme assay and subsequent identification of inhibitors of human immunodeficiency virus I replication", <i>J. Biol. Chem.</i> , 267(11), 1992, pp. 7224-39. See whole document.	12
X	Chemical Abstract 112:191580 & B. A. TROFIMOV et al., "Search for nonsteroidal anti-inflammatory drugs by using β -thiopropionic acid derivatives", <i>Khimico-Farmatsevticheskii Zhurnal</i> , 1989, 23(12), pp. 1463-5. See abstract and CAS RN 122815-13-8.	12
X	C. A. LANGNER et al., "4-Oxatetradecanoic acid is fungicidal for <i>Cryptococcus neoformans</i> and inhibits replication of human immunodeficiency virus I", <i>J. Biol. Chem.</i> , 267(24), 1992, 17159-69. See whole document.	12
X	Chemical Abstract 83:108314 & S. KANAO et al., "Syntheses of amino acid derivatives and their biological activities. I. Antiinfluenza activity", <i>Yagukaku Zasshi</i> , 1975, 95(4), pp. 397-401 See abstract and CAS RN 14379-40-9, 22220-07-1.	12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2005/000098**Supplemental Box**

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: II

The present application relates to the determination of "the full range of activities of the PUFAs and to identify naturally occurring members or to generate synthetic derivatives which have therapeutic potential" (see page 3, paragraph 2). I note that the formula defined by Claim 1 is so broadly drafted as to include long chain alkanes and alkenes, every known fatty acid and the applicant's acknowledged prior art at page 2 of the specification. It follows that Claim 19, which defines compounds *per se*, will lack novelty. A search is not feasible over the claimed matter.

Furthermore, the specification comprises little more than a list of known diseases. There is no support in the way of biological results to suggest that the entire range of diseases has been screened, nor even if the limited testing described in the examples would support the use of the compounds in the treatment of these other diseases. The claims are essentially useless as a reference on which a search may be generated. The only matter for which there is sufficient support in the specification and for which a search may be carried out are the compounds of Claim 12 when used for the specific uses described in the examples. Accordingly the search only adequately covers the matter of Claim 12 as it relates to the uses described in the examples. A limited search has also been carried out on the use of fatty acids in some of the treatments specified in the present claims, but it must be noted that the citations raised in this respect are a small selection from a very large answer set and cannot be considered an exhaustive search of the prior art.

Supplemental Box

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: III

The claims define the use of compounds of Formula I for the treatment of conditions selected from:

- (i) an NF κ B-related or associated condition;
- (ii) a PKC β -related or associated condition;
- (iii) vascular or immunological conditions.

The description and claims include a plethora of ailments, few of which appear to have any common biochemical relationship. Furthermore, there is no support in the specification for the majority of these ailments.

The claims also define compounds of the Formula I, the definition of which is so broad as to include unsubstituted hydrocarbons and other known matter (for example known fatty acids). Reference is made at page 2 to several previous PCT applications by the applicants, and present Claim 19 includes within its scope the compounds of these citations. Within the specification 4 broad genera of compounds are identified: the MP series; PT series; Lx series; and, MP-PT series. Each of these is known in the prior art, so the special technical feature of the invention that represents the advance over the prior art cannot be taken to reside in the compounds per se.

Accordingly the uses of the compounds represent the special technical feature. However the various uses described are distinct embodiments that are not linked by a single inventive concept. In particular, the numerous treatments described have no common biochemical origin. See for example the various cytokines and proteins defined in Claims 9 to 11, and the various treatments defined in Claims 13 to 18. There is no clear biochemical link between the matter defined in these claims. Accordingly, each of the defined treatments using each of the genera of fatty acid is taken to represent a separate invention. However most of the defined uses have such little support in the specification that an International Search has not been carried out for them.

A perusal of the examples indicates that the following studies have been carried out:

- (i) Use of MP5 and MP3 for the treatment of inflammation and immunosuppression by prevention of T-lymphocyte activation;
- (ii) Treatment of pain and analgesia using PT2;
- (iii) Activation of PKC by derivatives of the Lx series;
- (iv) Targeting of NF κ B using MP3;
- (v) Treatment of ailments related to PKC using MP5.

In view of the examples and the lack of support for the plethora of disease states defined by the claims, the present inventions are identified for which an International Search may be carried out:

- (1) treatment of an NF κ B related or associated condition using a compound of the MP series;
- (2) treatment of a PKC β -related or associated condition using a compound of the MP series;
- (3) treatment of a PKC β -related or associated condition using a compound of the Lx series;
- (4) treatment of pain and analgesia using a compound of the PT series; and,
- (5) treatment of inflammation and immunosuppression related to T lymphocyte activation by compounds of the MP series.

Search fees were paid for each of these inventions, but it is noted that these searches will only partially cover the matter defined in the claims, and particularly only the compounds of Claim 12 when used for the treatments described in the examples.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU2005/000098

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report			Patent Family Member				
WO	9611908	AU	36451/95	CA	2202503	CN	1163609
		EP	0869941	US	6376688		
WO	9613507	AU	37658/95	CA	2203791	CN	1167481
		EP	0804411	US	5998476		
WO	9738688	AU	24988/97	CA	2251780	EP	0904072
		GB	2328155	US	6262119		
WO	0121172	AU	76314/00	AU	76315/00	EP	1218000
		EP	1218333	US	2003078299	US	2003092762
		US	2004254240	WO	0121575		
WO	9611908	AU	36451/95	CA	2202503	CN	1163609
		EP	0869941	US	6376688	AU	76314/00
		AU	76315/00	EP	1218000	EP	1218333
		US	2003078299	US	2003092762	US	2004254240
		WO	0121172	WO	0121575		
WO	9008130	AU	48466/90	CA	2025107	EP	0409939
		HU	53594	US	5216023		
WO	02094764	CA	2446944	CN	1514822	EP	1389180
		GB	2376685	NZ	529023	US	2004242663
WO	03007876	US	2003022938	US	2004197399		
WO	03006007	EP	1425004	IT	MI20011483		
AU	22459/00	BR	0001201	CA	2305933	CN	1273239
		EP	1044966	FR	2792312	JP	2000344736
		NO	20001905	NZ	503514	SG	84577
		US	6511670	ZA	200001490		
US	5151534	AU	34522/89	DK	227789	EP	0342115
		FR	2631339	JP	2117654	PT	90492
		US	5268494	ZA	8903474		
WO	9958122	AU	49366/99	AU	49367/99	AU	54517/99
		AU	72403/98	BR	9910296	BR	9910297
		CA	2331393	CA	2331395	CA	2331408
		CN	1300211	CN	1300212	CN	1302204
		EP	1075258	EP	1075259	EP	1075260

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU2005/000098

EP	1284139	EP	1285652	HK	1034909
HK	1034912	NO	20005461	NO	20005462
NO	20005463	NZ	508045	NZ	508046
NZ	508047	US	6365628	US	6417232
US	6441036	US	2002198259	WO	9958120
WO	9958121	WO	9958123		
WO	0243728	AU	23162/02	BR	0115527
		EP	1351672	MX	PA03004427
		NO	20032054	NZ	525889
WO	9703663	AU	42726/96	CA	2226871
		EP	1232749	EP	1232750
EP	0345038	DK	267689	US	5093365
WO	9958120	AU	49366/99	AU	49367/99
		AU	72403/98	BR	9910296
		CA	2331393	CA	2331395
		CN	1300211	CN	1300212
		EP	1075258	EP	1075259
		EP	1284139	EP	1285652
		HK	1034912	HK	1034909
		NO	20005463	NO	20005462
		NZ	508047	NZ	508046
		US	6441036	US	6417232
		WO	9958122	WO	9958123
WO	0168582	AU	37835/01	BR	0108950
		CN	1419532	EP	1265838
		NO	20001123	NO	20024114
		US	2004213442	NZ	521137
WO	0121575	AU	76314/00	EP	1218000
		JP	2003509460	US	2003078299
WO	9958121	AT	245416	AU	49366/99
		CA	2331393	CN	1300211
		EP	1075259	ES	2204142
		NO	20005461	NZ	508045
		US	6417232	US	6441036

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX